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| 14. ABSTRACT The ex vivo manipulation of cells central to current approaches to cancer vaccines imposes a large economic and regulatory burden, dendritic cell modifications may be dependent on culture conditions and transient, and the vast majority of transplanted cells die following transplantation, leading to weak immune responses. The long-term objective is to bypass ex vivo cell manipulation in breast cancer vaccines, and instead develop effective material systems that program the immune system in situ. The specific hypothesis being addressed in this project is that a material system providing appropriate spatiotemporal presentation of GM-CSF, CpG oligonucleotides and specific tumor antigens to host dendritic cells (DCs) can effectively recruit, program and disperse host dendritic cells, and the programmed dendritic cells will be capable of stimulating specific T-cell populations and eliciting a strong anti-tumor response. In the previous funding cycle we demonstrated that polymers presenting appropriate cytokines and immunostimulatory cues can recruit large numbers of dendritic cells and regulate their activation. In this past year, we have demonstrated, in preliminary studies, that these polymeric vaccines can slow the progression of breast cancer growth, and reduce metastasis to the lungs. | | | | | |
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INTRODUCTION:

Cancer vaccines seek to prevent or treat breast cancer by activation of the immune system to destroy tumor cells. Ordinarily, the ability of tumor cells to stimulate an immune response is limited, in part, by weak expression of MHC-antigen complexes and costimulatory signals by antigen presenting cells that stimulate T-cell activation. Many experimental vaccines isolate and program dendritic cells (DCs) ex vivo by pulsing cultured cells with tumor associated antigens to bypass these issues, and introduce the programmed cells back into the patient where they may home to a lymph node, stimulate specific T-cell populations and elicit anti-tumor responses. While considerable progress has been made, the ex vivo manipulation of cells central to current approaches imposes a large economic and regulatory burden, DC modifications may be dependent on culture conditions and be transient, and the vast majority of transplanted cells die following transplantation, leading to weak immune responses. This application proposes a new approach to cancer vaccines, in which host cells are programmed in situ. We specifically propose to develop a material-based cancer vaccine that spatiotemporally controls the presentation of chemotactic factors and programming factors in situ in order to first recruit DCs, and secondly to program these cells with appropriate cues to elicit an effective antitumor response.

BODY:

Task 1: Developing system for GM-CSF tissue exposure to recruit dendritic cells

Completed in Year One with demonstration that sustained and localized release of GM-CSF from polymers can recruit large numbers of dendritic cells.

Task 2: Utilizing local CpG presentation to control maturation and lymph node homing of dendritic cells

Largely completed in Year One with demonstration that local presentation of CpG in concert with GM-CSF allows one to control the types and numbers of dendritic cells at the vaccine site, and their migration to the lymph nodes following antigen loading.

Task 3: Immunologic response to tumors

In the past year, two breast cancer models have been established in the laboratory, as a first step towards examining the efficacy of our approach to breast cancer prevention and treatment. The first model is the NT1 transplantable breast cancer model, as this represents a highly aggressive tumor model that demonstrates significant metastasis to the lungs. The second model is a transplantable and spontaneous breast cancer model that results from overexpression of Her2/neu, on a Balbc background.

Prophylactic vaccination studies were first performed in a transplantable tumor model. Vaccination of mice reduced the subsequent growth of NT1 tumors in mice, with approximately 25% of mice showing no tumor formation over the duration of the experiment (Fig. 1a). This preliminary experiment only utilized a partial vaccine formulation, and will be repeated with the complete vaccine including CpG oligonucleotides in the coming year. Similarly, vaccination of mice subsequently receiving Her2/neu overexpressing cells demonstrated a significant decrease in tumor size following vaccination with either the vaccine containing GM-CSF and antigen, with or without CpG (Fig. 1b). This study is the first of many to be performed over the coming year that will investigate the utility of the vaccine in this model

A therapeutic vaccination trial (NT1 model) was also performed with the complete vaccine (GM-CSF, tumor lysate, CpG), and animal survival and metastasis to the lungs were analyzed. Tumor growth was reduced with vaccination (Fig. 2a), although to a lesser extent than seen in our previous studies with melanoma. Lung metastasis were also reduced with vaccination (Fig. 2b).

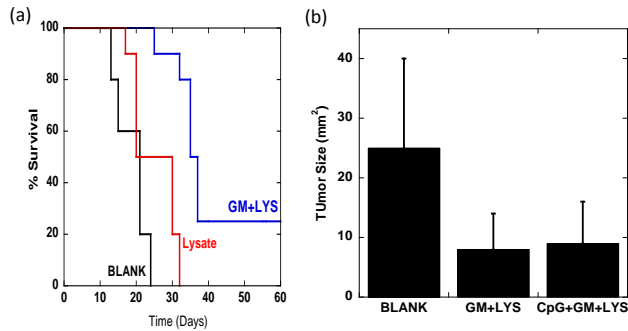


Fig. 1 Prophylactic vaccination against NT1 transplantable tumors. Female mice were vaccinated with PLG vaccines containing no agents (blank), tumor lysate alone (Lysate), or with GM-CSF and lysate (GM+Lys), and 14 days later 200,000 NT1 cells were injected into the mammary pad. Mice survival was followed over time.

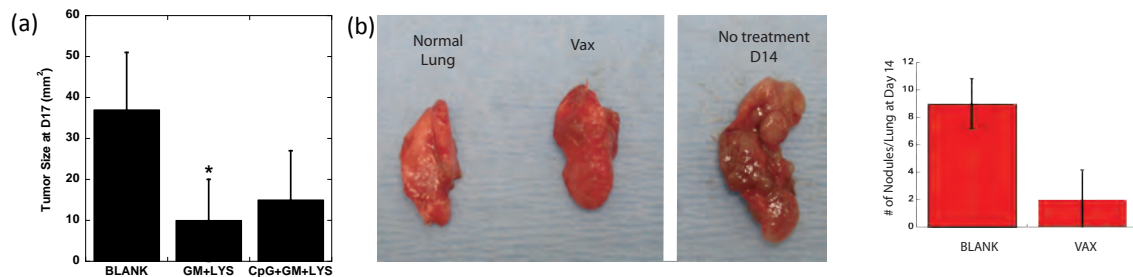


Fig. 2. Therapeutic vaccination against NT1 transplantable tumors. NT1 cells (200,000) were injected into the mammary pads of female Balbc mice, and the mice were subsequently vaccinated three days after cell injection. The size of the tumors was analyzed at day 17(a), and metastasis to lungs was also examined and quantified (b).

KEY RESEARCH ACCOMPLISHMENTS:

- Demonstrated that vaccine approach can slow tumor growth in two distinct models of breast cancer.
- First demonstration that this vaccine can inhibit lung metastasis.

REPORTABLE OUTCOMES:

- No new papers; we anticipate submitting 1-2 papers in the coming year
- Omar Ali was hired back to Harvard University, in order to aid in moving this vaccine approach into human clinical trials.

CONCLUSION:

The results to date indicate that material systems can recruit and activate large numbers of dendritic cells, and generate the types of dendritic cells and microenvironment consistent with generation of a destructive immune response. This orchestration of immune cell responses leads to significant protection in both prophylactic and therapeutic vaccination strategies in rodent models of breast cancer. These findings strongly support the premise underlying this project.

REFERENCES:

None

APPENDICES:

None

SUPPORTING DATA:

None